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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/485,071	02/03/2000	NORBERT O. REICH	30794.30USWO	1444

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EXAMINER	
LEWIS, PATRICK T	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 03/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/485,071	REICH ET AL.	
	Examiner	Art Unit	
	Patrick T. Lewis	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31,36,37,39 and 43-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31,36,37,39 and 43-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 February 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of claims relating to GC box pMET, SEQ ID NO: 10 in the reply filed on August 28, 2003 is acknowledged. The requirement was made FINAL in the Office Action dated April 14, 2004.

2. Claims 36-37, 39, 43-45 and 47-48 which were withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, have been amended to read upon the elected invention. An action on the merits of said claims is contained herein.

Applicant's Response Dated December 29, 2004

3. In the Response filed December 29, 2004, claims 44-46 were amended. Claims 31, 36, 37, 39 and 43-48 are pending. An action on the merits of claims 31, 36, 37, 39 and 43-48 is contained herein below.

4. Applicant's request for reconsideration of the finality of the rejection of the last Office Action is persuasive and, therefore, the finality of that action is withdrawn.

5. The rejection of claims 31 and 46 under 35 U.S.C. 103(a) as being unpatentable over the combination of Flynn et al. *Biochemistry* (1986), Vol. 35, pages 7308-7315 (Flynn) and Billing-Medal et al. US 6,183,952 (Billing) is maintained for the reasons of record set forth in the Office Action dated October 29, 2004.

Rejections of Record Set Forth in the Office Action Dated October 29, 2004

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. Claims 31 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Flynn et al. *Biochemistry* (1986), Vol. 35, pages 7308-7315 (Flynn) and Billing-Medal et al. US 6,183,952 (Billing).

8. Applicant's arguments filed December 29, 2004 have been fully considered but they are not persuasive. Applicant argues that: 1) the examiner has not pointed to a teaching, in Flynn or elsewhere, that the claimed oligonucleotide is linked to tumor development; 2) even if it were true that Flynn taught a link between the oligonucleotide of SEQ ID NO: 10 and tumor development, that would not suffice to provide motivation to modify the oligonucleotide of SEQ ID NO: 10 to incorporate phosphorothiolate linkages or to add a pharmaceutically acceptable carrier, unless it was known that this alleged link between the oligonucleotide and tumor development involved an inhibitory effect of the oligonucleotide on tumor development; and 3) the examiner has not stated where in the prior art it is taught that the synthetic oligonucleotide of applicant's claims is useful as an antisense oligonucleotide. Applicant further asserts that the examiner has confused "substrate" of DCMTase with "inhibitor" of DCMTase.

Applicant's attention is directed to page 7308 of Flynn. Flynn teaches these substrates were designed to mimic DNA transcriptional cis elements previously reported to have cytosine C-5-methylated regulation. The rate-limiting step for these substrates is the methylation step itself. Methylation of DNA at cytosine (5-mC)[1] occurs in most

biological kingdoms. The function of cytosine methylation in mammals mainly involves positive and negative transcriptional control and appears predominantly in the minimal context of the CpG dinucleotide. A concerted progression of maintenance methylation, demethylation, and *de novo* methylation of the entire genome is envisioned as a mechanism for the final genomic expression configuration of a terminally differentiated cell. DNA methylation is catalyzed by S-adenosyl-L-methionine (AdoMet)-dependent, DNA (cytosine-5-)methyltransferase (DCMTase, EC 2.1.1.37). An essential role for the control of methylation patterns by the DCMTase has been shown by specific gene disruption in mice. Amplification of DCMTase gene induces tumorigenic transformation of NIH 3T3 mouse fibroblasts; correspondingly, human neoplastic cells and cells derived from different stages of colon cancer expresses up to 200-fold higher levels of DCMTase than normal. Conversely, expression of antisense DCMTase mRNA is the adrenocortical carcinoma cell line Y1 inhibits tumorigenesis. The anticancer agent 5-azadeoxycytidine functions by inhibiting the DCMTase, and DCMTase activity contributes substantially to tumor development in a mouse model of intestinal neoplasia.

Flynn further explains on pages 7309-7310 that a precise functional description of the enzyme is essential for understanding how DCMTase methylation and for the design of novel anticancer strategies based on regulation of the enzyme. The primary focus on the Flynn study was on the two DNA sequences shown in Table 1 (GC-box b^{met} reads upon a synthetic oligonucleotide of 30 nucleotides in length which comprises a 5mCpG dinucleotide and the nucleotide sequence shown in SEQ ID NO: 10). The two sequences are thought to differentially regulate gene expression, depending on the

methylation state of a single CpG dinucleotide. One sequence contains the cyclic AMP responsive element (CRE), and the other contains a GC-box, which is an Sp1 transcription factor recognition element (GC-box). In each case, the regulatory element was imbedded within a 30-nucleotide sequence with an identical flanking sequence. The single-stranded and unmethylated double-stranded versions of these substrates are methylated at a slower but liner rate (Figure 3), whereas the hemimethylated substrates (CRE a^{met}/b and GC-box a/b^{met}) show a burst of product formation (Figures 4 and 5) followed by a linear rate of product formation (page 7313). Methylation of CRE a^{met}/b and GC-box a/b^{met} must therefore be relatively rapid and followed by a slower step. The discrimination of the DCMTase for various substrates is quantitively shown by the specificity constants in Table 3 (page 7314). The enzyme has an approximate 2-fold preference for the GC-box a/b^{met} sequence over the CRE a^{met}/b sequence, and this preference is not observed with the unmethylated versions of these substrates.

The examiner acknowledges that GC-box b^{met} as taught by Flynn does not contain a phosphorothiolate nucleotide as instantly claimed; however, contrary to applicant's assertions, it would have been obvious to incorporate artificial internucleotide linkages into the GC-box b^{met} oligonucleotide. Billing teaches that antisense technology can be used to reduce gene expression through triple-helix formation or antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA (column 26). For example, the 5' coding portion of the polynucleotide sequence, which encodes the polypeptide of the invention of Billing, is used to design an antisense RNA oligonucleotide of from 10 to 40 base pairs in length.

A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription, thereby preventing transcription and the production of the BU101 polypeptide. Antisense oligonucleotides act with greater efficacy when modified to contain artificial internucleotide linkages which render the molecule resistant to nucleolytic cleavage. Such artificial internucleotide linkages include, but are not limited to, methylphosphonate, phosphorothiolate and phosphoroamydate internucleotide linkages.

Applicant appears to have confused the requirements of 35 U.S.C. 102 and 103. 35 U.S.C. 103(a) does not require that the prior art disclose the instantly claimed oligonucleotide or its usefulness as an antisense oligonucleotide. Flynn's explanation on pages 7309-7310 that a precise functional description of the enzyme is essential for understanding how DCMTase methylation and for the design of novel anticancer strategies based on regulation of the enzyme is seen to be sufficient motivation to modify the internucleotide linkages and provide a pharmaceutical composition as instantly claimed. Obviousness does not require absolute predictability. The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. In the instant case, Flynn explicitly teaches that the substrates were designed to mimic DNA transcriptional cis elements previously reported to have cytosine C-5-methylated regulation. In the absence of evidence of some unexpected result or limitation that would tip the scales of patentability in applicant's favor, the instantly claimed invention is prima facie obvious.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

12. Claims 36-37, 39, 43-45 and 47-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Flynn et al. *Biochemistry* (1986), Vol. 35, pages 7308-7315 (Flynn) and Billing-Medal et al. US 6,183,952 (Billing).

Claims 36, 37, 39, and 43-45 are drawn to a synthetic oligonucleotide of at least 26 nucleotides in length comprising a 5mCpG dinucleotide, wherein the 5mC is a C-5-methylcytosine, and which comprises a nucleotide sequence shown in SEQ ID NO: 10, wherein the synthetic oligonucleotide comprises a phosphorothiolate nucleotide. Claims 36, 37 and 39 further limit the oligonucleotide length. Claims 43-45 are dawn to a pharmaceutically acceptable salt. Claims 47 and 48 are drawn to a pharmaceutical composition comprising a synthetic oligonucleotide of at least 26 nucleotides in length comprising a 5mCpG dinucleotide, wherein the 5mC is a C-5-methylcytosine, and which comprises a nucleotide sequence shown in SEQ ID NO: 10, wherein the synthetic oligonucleotide comprises a phosphorothiolate nucleotide. Claim 48 further limits the length of the oligonucleotide.

Flynn teaches these substrates were designed to mimic DNA transcriptional cis elements previously reported to have cytosine C-5-methylated regulation (page 7308). The rate-limiting step for these substrates is the methylation step itself. Methylation of DNA at cytosine (5-mC)[1] occurs in most biological kingdoms. The function of cytosine methylation in mammals mainly involves positive and negative transcriptional control and appears predominantly in the minimal context of the CpG dinucleotide. A concerted progression of maintenance methylation, demethylation, and *de novo* methylation of the entire genome is envisioned as a mechanism for the final genomic expression configuration of a terminally differentiated cell. DNA methylation is catalyzed by S-adenosyl-L-methionine (AdoMet)-dependent, DNA (cytosine-5-)methyltransferase (DCMTase, EC 2.1.1.37). An essential role for the control of methylation patterns by

the DCMTase has been shown by specific gene disruption in mice. Amplification of DCMTase gene induces tumorigenic transformation of NIH 3T3 mouse fibroblasts; correspondingly, human neoplastic cells and cells derived from different stages of colon cancer expresses up to 200-fold higher levels of DCMTase than normal. Conversely, expression of antisense DCMTase mRNA is the adrenocortical carcinoma cell line Y1 inhibits tumorigenesis. The anticancer agent 5-azadeoxycytidine functions by inhibiting the DCMTase, and DCMTase activity contributes substantially to tumor development in a mouse model of intestinal neoplasia.

Flynn further explains on pages 7309-7310 that a precise functional description of the enzyme is essential for understanding how DCMTase methylation and for the design of novel anticancer strategies based on regulation of the enzyme. The primary focus on the Flynn study was on the two DNA sequences shown in Table 1 (GC-box b^{met} reads upon a synthetic oligonucleotide of 30 nucleotides in length which comprises a 5mCpG dinucleotide and the nucleotide sequence shown in SEQ ID NO: 10). The two sequences are thought to differentially regulate gene expression, depending on the methylation state of a single CpG dinucleotide. One sequence contains the cyclic AMP responsive element (CRE), and the other contains a GC-box, which is an Sp1 transcription factor recognition element (GC-box). In each case, the regulatory element was imbedded within a 30-nucleotide sequence with an identical flanking sequence. The single-stranded and unmethylated double-stranded versions of these substrates are methylated at a slower but liner rate (Figure 3), whereas the hemimethylated substrates (CRE a^{met}/b and GC-box a/b^{met}) show a burst of product formation (Figures 4

and 5) followed by a linear rate of product formation (page 7313). Methylation of CRE a^{met}/b and GC-box a/b^{met} must therefore be relatively rapid and followed by a slower step. The discrimination of the DCMTase for various substrates is quantitively shown by the specificity constants in Table 3 (page 7314). The enzyme has an approximate 2-fold preference for the GC-box a/b^{met} sequence over the CRE a^{met}/b sequence, and this preference is not observed with the unmethylated versions of these substrates.

Flynn differs from the instantly claimed invention in that Flynn teaches phosphoramidite linkages instead of phosphorothiolate linkages as instantly claim and Flynn does not explicitly teach pharmaceutically acceptable salts or pharmaceutical compositions.

Billing teaches that antisense technology can be used to reduce gene expression through triple-helix formation or antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA (column 26). For example, the 5' coding portion of the polynucleotide sequence, which encodes the polypeptide of the invention of Billing, is used to design an antisense RNA oligonucleotide of from 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription, thereby preventing transcription and the production of the BU101 polypeptide. Antisense oligonucleotides act with greater efficacy when modified to contain artificial internucleotide linkages which render the molecule resistant to nucleolytic cleavage. Such artificial internucleotide linkages include, but are not limited to, methylphosphonate, phosphorothiolate and phosphoroamydate internucleotide linkages.

It would have been obvious to incorporate artificial internucleotide linkages into the GC-box b^{met} oligonucleotide and their corresponding pharmaceutically acceptable salts. It would have also been obvious to provide said oligonucleotides as pharmaceutical compositions. Flynn's explanation on pages 7309-7310 that a precise functional description of the enzyme is essential for understanding how DCMTase methylation and for the design of novel anticancer strategies based on regulation of the enzyme is seen to be sufficient motivation to modify the internucleotide linkages and provide a pharmaceutical composition as instantly claimed. Obviousness does not require absolute predictability. The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. In the instant case, Flynn explicitly teaches that the substrates were designed to mimic DNA transcriptional cis elements previously reported to have cytosine C-5-methylated regulation.

Conclusion

13. Claims 31, 36, 37, 39 and 43-48 are pending. Claims 31, 36, 37, 39 and 43-48 are rejected. No claims are allowed.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Contacts

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick T. Lewis whose telephone number is 571-272-0655. The examiner can normally be reached on Monday - Friday 10 am to 3 pm (Maxi Flex).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Examiner
Art Unit 1623

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